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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,220	10/15/2003	Xu Wu	021288-001820US	8079

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/687,220	WU ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-46 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9,11-35 and 42-46 is/are rejected.

7)☒ Claim(s) 10 and 36-41 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 15 October 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Montgomery.

See VId, corresponding to R^6 as p-Cl, R^4 = benzyl, R^1 = H, R^5 = H.

Claims 1 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Kelley.

See II, and species 6, 9, 12, 14, 15, 21, 24 and 25. These correspond to R^6 as para or meta substituted alkyl, Halo, or dimethylamino, R^4 = benzyl, R^1 = Cl, R^5 = H. The compounds are antivirals.

Claims 1 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Imbach (1999).

See species 3, 5-7, 11-15. These correspond to R^6 as para or meta Cl or F, R^4 = ethyl, R^1 = Cl, Hydroxyethyl, aminoethyl, and aminocyclohexylamino, R^5 = H. The compounds are antiproliferative agents.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Basyouni.

See 2a, corresponding to R^6 as p-methyl, R^4 = tolyl, R^1 = H, R^5 = H.

Claim 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by US 6255485.

See Column 23 scheme last and next to last structure. Note specifically examples 5 and 6, which correspond to R^6 as m-Cl, R^4 = isopropyl (thus meeting the claim 4 requirement as well), R^1 = F or hydroxy substituted pentylamino, R^5 = H.

Claims 1, 11-35 and 42-46 is rejected under 35 U.S.C. 102(b) as being anticipated by US 2002/0016329.

See Formula I, the choice in paragraph 0005, where k = 2, which corresponds in the claims to R6 = choice 4, i.e. the optionally substituted amino sulphonyl choice. See species at page 20, lines 7-8, corresponding to R^6 as p-butylaminosulfonyl, R^4 = ethyl, R^1 = Cl, R^5 = H. Note also claim 11, species 6-7, which have R^6 as p-(butyl or isobutyl) aminosulfonyl, R^4 = ethyl, R^1 = aminocyclohexylamino, R^5 = H. Note many additional examples in paragraph 321, such as examples 1-3, which have R^1 = aminocyclohexylamino where the cycohexanes is substituted by $C(O)NH_2$. This corresponds in the claims to the next to last R2a choice when R2b = H. The utility is the same as is claimed here.

Claims 1 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 200071543 A1.

See example 108, both the final product and the starting material at lines 4-5 of page 167. These correspond to R^6 as para sulfonamide ($-SO_2NH_2$), R^4 = cyclopentyl, R^1 = aminocyclohexylamino and Cl respectively, R^5 = H. The compounds are antivirals.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to

> be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Imbach (1999) or US 2002/0016329.

The species in Imbach (1999) and US 2002/0016329 having R^4 = ethyl render obvious the isopropyl of claim 4 as a homolog. Compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. As was stated in *In re Grose*, 201 USPQ 57, 63, "The known structural relationship between adjacent homologues, for example, supplies a chemical theory upon which a prima facie case of obviousness of a compound may rest." The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methyl groups. See *In re Wood,* 199 USPQ 137; *In re Hoke,* 195 USPQ 148; *In re Lohr,* 137 USPQ 548; *In re Magerlein,* 202 USPQ 473; *In re Wiechert,* 152 USPQ 249; *Ex parte Henkel,* 130 USPQ 474; *In re Jones*, 74 USPQ 152, 154; *Ex Parte Fischer* 96 USPQ 345; *In re Fauque,* 121 USPQ 425; *In re Druey,* 138 USPQ 39. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness. Note also *In re Jones*, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie*

obviousness"; one of those listed is "adjacent homologues and structural isomers". Similar is *In re Schechter and LaForge*, 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." Note also *In re Deuel* 34 USPQ2d 1210, 1214 which states, "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." See also MPEP 2144.09, second paragraph.

Further, US 2002/0016329 teaches the equivalence of the two. R3 is taught to be lower alkyl in many places, e.g. paragraph 0217.

Claims 4-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 200071543 A1.

The claims call for the cyclohexyl, whereas the example 108 species has the cyclopentyl. However, the reference teaches the equivalence of these two. Note that R2 can be cycloalkyl generally, and page 4, line 17 names these two rings, thus teaching that these are alternatively useable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 11-35, 42-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The commas must be removed from the formula. That is, something like N(A, B) should be written as N(AB).
2. In Heterocycle, such as is formed from R3, of what types? "Heterocyclic" is indefinite. What is the size of the ring? What is the number and nature of the heteroatoms? Can the ring be fused or spiroconnected to another ring, and if so, what kind of ring? Can the ring be bridged? Unsaturated? Cf. *In re Wiggins*, 179 USPQ 421, 423.
3. Some of the terms are written backwards. This "alkylhalo" in R7a should be haloalkyl. Likewise alkylhydroxy, alkylaryl and alkylheterocycle in R4, etc.
4. The last R4 choice in claim 8 is in error. This is alkyl substituted by cycloalkyl, but cycloalkyl is not permitted for R4a. Likewise the next to last species in claim 9.
5. Likewise for the third choice. R4a is not permitted to be phenoxy.
6. The next to last choice in claim 8 is not permitted either. It has 3 carbons in the chain, but claim 1 permits only two (see page 46, line 18). Likewise the 6th to last species in claim 9.
7. The term "alkyl" has been rendered indefinite by the specification. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning

repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The meanings quoted by applicants are not the usual meaning at all. Alkyl is a group of the formula $-C_nH_{2n+1}$, as is set forth in such sources as Hack's Chemical Dictionary and Hawley's Condensed Chemical Dictionary, or any textbook of organic chemistry. As such it cannot be unsaturated, rings or have heteroatoms. Since both rings and unsaturation are permitted, groups like phenyl would be embraced. According to paragraph 0021, the term covers not only terms with unsaturation, and with rings, but also "heteroalkyl", a term whicvh according to paragraph 0024 is broad enough to embrace choices like SCH_3 or OH. These are not alkyl groups. It appears that virtually anything other than H will fall into the definition of alkyl.

8. A similar problem occurs with aryl and heteroaryl. Judging from the first sentence of paragraph 0027, aryl does not have to be aromatic, and would cover a terms such as cyclooctadiene or dihydropyridine. These are not an aryl or heteroaryl.

Claims 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for most choices, does not reasonably provide enablement for the third choice in claim 8, the last two choices in claim 8, and the 6th to last choice in claim 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. See points 4-6 above. These choices are not within Formula I, to which the utility is tied. Hence, these choices do not fall within the utility umbrella, and as a result, the specification does not teach how to use them.

Claims 42, 45 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of bone disorders generally is not enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Because of the broad scope of R6, R4 and R1, billions of compounds are covered.

(b) Scope of the diseases covered. The scope of bone disorders is immense. The term includes common bone disorders such as Paget's disease, hereditary multiple exostosis, and osteoporosis. It also includes Dysplasias including Osteogenesis imperfecta, Osteopoikilosis, Osteopetrosis (Albers-Schoenberg disease),

achondroplasia, Osteochondromatosis, Caffey's disease, Lenz-Majewski syndrome, Melorheostosis, metaphyseal dysplasia (Pyle disease), pyknodysostosis, sclerosing diaphyseal dysplasia (Camurati-Engelmann Disease), spondyloepiphyseal dysplasia and many others. It includes dense bones disorders, including axial osteomalacia, fibrogenesis imperfecta ossium, sarcoidosis and tuberous scelrosis. Other bone disorders include cleidocranial dysostosis, coxa plana, Hand-Schueller-Christian disease, brachydactyly, calcium pyrophosphate deposition disease (CPPD), Wormian bones, tibia vara (Blount disease), cervical spine fusion (ankylosis), Crouzon syndrome, slipped capital femoral epiphysis (SCFE), celery-stalk metaphyses, Bankart deformity, Ollier disease, craniosynostosis, Erlenmeyer flask deformity, ivory vertebral body, spheroid calcification, acro-osteolysis, Caffey disease, cherubism, Sever disease, Sprengel deformity, Panner disease, osteogenesis imperfecta, Letterer-Siwe disease, Pott's disease, Scheuermann disease, sabre-shin deformity, basilar invagination, degenerative disc disease, block vertebra, Kohler disease, hyperostosis frontalis interna, diastrophic dwarfism, osteochondrosis, posterior vertebral scalloping, multicentric reticulohistiocytosis, osteitis fibrosa, vertebra plana, Hill-Sachs deformity, Kienbock disease, spontaneous osteolysis, Osteochondritis dissecans, Osteomyelitis and many, many more. Included also are bone tumors, including Osteosarcomas (osteoblastic, chondroblastic, fibroblastic, telangiectatic, and others), Hemangiosarcoma, Periosteal chondrosarcoma, Periosteal fibrosarcoma, Maxillary fibrosarcoma, Parosteal osteosarcoma, Periosteal osteosarcoma, Malignant mesenchymoma, Liposarcoma, synovial sarcoma, Osteochondroma, Hemangioma, Myxoma of the jaw, Ossifying fibroma, Osteoma, Giant cell tumor of bone, multiple myeloma, solitary myeloma,

reticulum cell sarcoma, malignant fibrous histiocytoma, desmoblastic fibroma of the bone, periosteal fibroma, lipoma, Hemangioendothelial sarcoma, Ewing's sarcoma, chondroblastoma, and Multilobular tumor of bone. There are also tumor-like lesions, including osteoid Osteoma, non-osteogenic Fibroma, benign osteoblastoma, Solitary bone cyst, Juxtacortical bone cyst, Myositis ossificans, Villonodular synovitis and Epidermoid cyst of the phalanx. There are also secondary malignant deposits in bone.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information appears to be missing.

(4) State of the Prior Art: These are anilino-purines with a particular substitution pattern. . So far as the examiner is aware, no anilino-purines of any kind are in use for the treatment of bone disorders. Also, one skilled in the art knows that bone disorders can arise from a huge assortment of unrelated causes. These include Ehlers-Danlos syndrome; galactosemia; cirrhosis; vitamin D malabsorption arising from GI disorders such as celiac disease, from pancreatic insufficiency, from biliary atresia and other sources; abnormal vitamin D metabolism arising from e.g. anticonvulsant therapy, chronic renal failure, etc.; hyperparathyroidism and hypoparathyroidism and pseudohypoparathyroidism; Marfan syndrome; fluorosis (excessive fluoride intake); ochronosis; lead poisoning; cadmium poisoning; Morquio's disease; Cushing's disease;

Gaucher disease; tyrosinemia; homocystinuria; scurvy; ToRCHS syndrome; renal osteodystrophy; Hypertrophic osteoarthropathy; Klippel-Feil syndrome; sickle cell anemia; glycogen storage disease; Niemann-Pick disease; hyperuricemia; renal transplantation; hemophilia; gout; histiocytosis X; Tuberculosis; hypervitaminosis A and D; frostbite; burns; leprosy; polyvinylchloride exposure; progeria; acromegaly; basal cell nevus syndrome; Erdheim-Chester disease; psoriasis; Ligna-Franconi Diseasesteroids; shoulder dislocation; juvenile rheumatoid arthritis; Wilson's Disease; hypophosphatasia and pseudo hypophosphatasia; ingestion of phosphate binding antacids, and of mineralization inhibitors such as Etidronate; dietary deficiencies in phosphate and calcium; brain tumors; alcohol abuse; bone fracture; bacterial or fungal infection; diabetes; caisson disease; irradiation; hemodialysis; hepatitis C; milk-alkali syndrome; carbonic anhydrase II deficiency and many, many more. The secondary malignant deposits in bone arise from primary malignancies in the thyroid, breast, bronchus, kidney and prostate. There are a wide assortment of genetic problems, many of them poorly understood, which cause bone disorders. And often, the cause is unknown. For example, Paget's disease is the second most common disorder of the bone, and its origin is unknown.

(5) Working Examples: There are none to the actual treatment of disease.

(6) Skill of those in the art: The skill level varies greatly according to which disorder is involved. For e.g. osteoporosis the skill level is good. For many others, the skill level is extremely low, as there have been no successful pharmacological treatments. An example is the assorted osteosarcomas; no chemotherapy has even been demonstrated as a successful mode.

(7) The quantity of experimentation needed: In view of the extreme diversity of such disorders, the known difficulty of treating bone disorders with medicinals, the level of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claims 10, 36-41 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Specification

The missing text is needed for paragraph 0001. The abstract is objected to as too vague. Suggested is Formula I, along with the definitions for R6 and R4.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (571)272-0674. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Berch
Primary Examiner
Art Unit 1624

12/13/04